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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/160,067	09/24/98	GUNZBURG	W	GSF98-04A

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EXAMINER	
HUTSON,R	
ART UNIT	**PAPER NUMBER**
1652	12

DATE MAILED: 10/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/160,067	Gunzburg et al.
Examiner	**Group Art Unit**
Richard Hutson	1652

☐ Responsive to communication(s) filed on _____

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-22 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-22 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment of claims 1, 3-7, 9, 10-12, 16, 17 and 20 and the addition of new claims 21 and 22 is acknowledged. Claims 1-22 are at issue and are present for examination.

Applicants' arguments filed on 7/21/2000, paper No. 11, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on 3/27/96. It is noted, however, that while applicant has filed a certified copy, a translation of the DK 0352/96 application as required by 35 U.S.C. 119(b) has not been filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11-19, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing a tumor comprising the direct insertion of the capsule into the tumor wherein expression of the DNA sequence results in an inhibition in tumor growth or a decrease in tumor size and a pharmaceutical kit comprising said capsule, does not reasonably provide enablement for a method of treating a tumor comprising administering to a subject in need thereof a therapeutically effective amount of the capsule of claim 1 and, either

simultaneously or with a time span, a prodrug which is activated by cytochrome P450. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is stated in the previous office action as it applied to claims 11-15 and 20.

Applicant amended claim 11 to recite a method of treating a tumor comprising administering to a subject in need thereof a therapeutically effective amount of the capsule according to claim 1 and either simultaneously or with a time span, a prodrug which is activated by cytochrome P450. Further, applicants amended claim 20 to depend from claim 10. While this amendment overcomes the previous rejection with respect to claim 20, claims 11-19 remain rejected because the scope of claim 11 is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods of administering said capsule broadly encompassed by the claims. The specification only teaches a method of decreasing a tumor comprising the direct insertion of the capsule into the tumor wherein expression of the DNA sequence results in an inhibition in tumor growth or a decrease in tumor size. As discussed in the previous office action, the route of administration of said capsule encapsulating a cytochrome P450 producing cell effects the success of any method of treating a disease, and thus predictability of those routes of administration of said capsule which would result in successful treatment of said disease, encompassed by the claim are unpredictable and would require undue experimentation to one of ordinary skill in the art. The guidance in the specification as seen in example 10, only provides guidance for the direct insertion of capsules encapsulating cytochrome

P450 producing cells into tumors. There is no guidance for other results of administration. In particular there is no evidence that by systemic administration sufficient capsules would reach the target tumor to have any affect on the tumor. At no place does the specification discuss methods of "homing" the encapsulated cells to a particular tumor, organ or tissue.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including means of administration of a capsule encapsulating cytochrome P450 expressing cell. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those relevant diseases or disorders as well as method of administering said capsule is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 5 as amended is rejected for containing new matter which is not supported by the original specification, specifically "said capsule is formed from counter-charged polyelectrolytes. It is acknowledged that on page 12, lines 15-28 of the specification, the applicants discuss in

detail the encapsulation technology of the instant invention, including the described "electrolyte complex (e.g. from alginate and polylysine or more preferably, cellulose sulphate and polydimethyldiallylammonium chloride) or other porous structures (such as polyamides, polysulfones)." This does not support the broader limitation of a capsule formed from counter-charged polyelectrolytes.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 9, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly amended claim 1 is rejected because the limitation, "wherein the prodrug molecules are converted into active drug molecules by cytochrome P450", is confusing because this limitation does not describe the capsule encapsulating a cytochrome P450 expressing cell, but rather appears to describe a method.

Claim 9 (claim 21 dependent from) is rejected because it is unclear as to the intent of the applicant. Newly amended claim 9 recites "The capsule according to Claim 1 wherein the cytochrome P450 2B1." It could be viewed that there is no antecedent basis in claim 1 for "cytochrome P450 2B1", or is the intention of the applicant to further limit the cytochrome P450

of claim 1 to cytochrome P450 2B1. For the purpose of compact prosecution the latter is how the claim is interpreted for examination purposes.

Claim 22 is rejected because it is unclear as to the intent of the applicant. Newly added claim 22 recites "The capsule according to Claim 1 wherein the cytochrome P450 is present in a mammalian expression vector." Literal interpretation of this claim means that the cytochrome P450 **protein** itself is in a mammalian expression vector. It is not normal for one of ordinary skill in the art to place a protein in an expression vector, unless applicants intent is to refer to the instant capsule as a "expression vector". It is the interpretation of the examiner that applicants intent was that the nucleic acid or gene encoding cytochrome P450 is in a mammalian expression vector and for the purpose of compact prosecution this is how the claim will be interpreted for examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-20 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Saller et al. (WO 97/01357).

The rejection is stated in the previous office action as applied to claims 1-5, and 7-20.

As discussed in the previous office action, Saller et al. teach the use of encapsulated cells producing viral particles containing a replication defective retroviral construct carrying the cytochrome P450 gene, pLX125 (Example 4), for the treatment of tumors.

Applicants traverse this rejection on the basis that as amended applicants claimed invention relates to a capsule encapsulating a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450. Applicants further traverse that unlike the Saller et al. reference, the applicants teach expression of the cytochrome P450 gene within the encapsulated cells which have been transduced with an expression vector comprising the cytochrome P450 gene and that the cytochrome P450 cannot pass out of or be delivered from applicants claimed capsule. Applicants further state that the prodrug upon administration enters the capsule and is converted into its active form by the cytochrome P450. The activated drug is then delivered from the capsule and directly attacks the tumor. This argument is not found persuasive. It is acknowledged that the Saller et al. reference does not specifically teach the expression of cytochrome P450 within the encapsulated cells, and a mechanism of action whereby the prodrug upon administration enters the capsule and is converted into its active form by the cytochrome P450 expressed in the encapsulated cells. This is in fact an inherent characteristic of the encapsulated cells taught by Saller et al. Further it is noted that while during the course of this traversal the applicants have attempted to clarify the invention, the claims as currently amended

still remain anticipated by the Saller et al. reference. Specifically, the encapsulated cells taught by Saller et al. express cytochrome P450 protein, and the capsule allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450.

Therefore, claims 1-5, 7-20 are anticipated by Saller et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 8, 9, 10, 11, 12 and 15-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. (Human Gene Therapy 5: 969-978, 1994) and Tai et al (FASEB Journal 7: 1061-1069, 1993).

The rejection is stated in the previous office action as applied to claims 1, 8, 9, 15-19.

As discussed in the previous office action, Wei et al. teach that the addition of cytochrome P450 2B1-producing fibroblasts followed by CPA administration, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors in the brains of athymic mice, previously seeded with rat C6 gliomas. Tai et al. teach an alternate strategy of gene therapy that involves immunoisolating genetically modified cells in a biocompatible

membrane (a capsule), thereby introducing a system that can provide sustained delivery of the desired gene product to a tissue or group of cells.

Applicants traverse this rejection on the basis that the prior art does not provide "Both the suggestion and the reasonable expectation of success...". The applicants further state that the combined teachings of Wei et al. and Tai et al. do not teach or even suggest encapsulating cells which express "an integral membrane protein" such as cytochrome P450 which integrates into the membrane of the cells expressing the protein, and thus remains in the capsule. The applicants further state that a person of skill in the art would not be motivated to combine the teachings of Wei et al. and Tai et al. for the purpose of encapsulating a cytochrome P450 expressing cell, because cytochrome P450 would not "pass out" of capsules comprising such cells and thus it would not be possible to introduce cytochrome P450 into tumor cells as directed by Wei et al. This argument is not found persuasive. While it is acknowledged that one of ordinary skill in the art would not combine the teachings of Wei et al. and Tai et al. for the purpose of encapsulating a cytochrome P450 expressing cell because cytochrome P450 would not "pass out" of said capsule, one of ordinary skill in the art would have motivation to combine the teachings of Wei et al. and Tai et al. for the purpose of encapsulating a cytochrome P450 expressing cell because as taught by Wei et al. intrathecal administration of cytochrome P450 producing fibroblasts, followed by CPA, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors (See abstract of Wei et al. and page 973). Furthermore, the applicant points out that the cited art does not teach or suggest that a prodrug would enter the capsules comprising cells which express

cytochrome P450 etc... It is noted that the claims as currently amended do not limit the invention to such a mechanism of action.

Applicants further assert that the finding that cytochrome P450 expressing cells survive for a period of time, that the enzyme is not only expressed but also integrated into the membrane and that the enzyme indeed converts prodrug molecules into drug molecules must be regarded as a surprising and unexpected result. This argument also is not found persuasive because it is not surprising that an encapsulated cytochrome P450 expressing cell survives nor is it surprising that the cytochrome P450 protein is integrated into the cell membrane and converts prodrug molecules into drug molecules. Tei et al. teach that encapsulation of genetically modified fibroblasts may represent a useful delivery system for recombinant proteins in vivo, and Wei et al. teach that fibroblasts transfected with plasmids encoding cytochrome P450 successfully express the cytochrome P450 protein which then activate the anticancer drug CPA.

Newly added claims 21 and 22 are also included in this rejection because Wei et al. teach that the cytochrome P450 2B1 gene is derived form rat, and it would be obvious to express the cytochrome P450 gene in a mammalian expression vector so as to get production in the target cell, a mammalian cell.

Therefore, claims 1, 5, 8, 9, 10, 11, 12 and 15-22 are made obvious by Wei et al. and Tai et al.

Claims 2, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. and Tai et al. as applied to claim 1, 8, 9, 15, 16, 17, 18 and 19 above in previous office action, and further in view of Merten et al. (Cytotechnology 7(2): Abstract , 1991).

Merten et al. teach a method for encapsulation of mammalian cells using capsules comprising cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride (PDMDAAC).

This rejection is stated in the previous office action as it applied to claim 2.

Applicants traverse this rejection as above 103 rejection on the basis that the prior art does not provide "Both the suggestion and the reasonable expectation of success..." and that Merten et al. does not provide what is lacking from the combined teachings of Wei et al. and Tai et al. This argument is not found persuasive for the same reasons as above, and the additional limitation of capsules comprising cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride (PDMDAAC) is taught by Merten et al. as well as the motivation for using such a material.

Therefore, Wei et al., Tai et al. and Merten et al. make obvious claims 2, 4 and 5.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13 and 15 of copending Application No. 08/996,460. Although the conflicting claims are not identical, they are not patentably distinct from each other because they claim common subject matter, A capsule encapsulating a cytochrome P450 producing cell, said capsule comprising a porous membrane which allows prodrug to pass into the capsule, wherein the cytochrome P450 producing cell is a packaging cell comprising a retroviral vector carrying the cytochrome P450 gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants traverse this provisional rejection as they traverse the 102 rejection based upon WO 97/01357 above. This argument is not found persuasive for the above reasons of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Richard Hutson Ph.D.
10/5/2000